JOURNAL OF combinatorial CHEMISTRY

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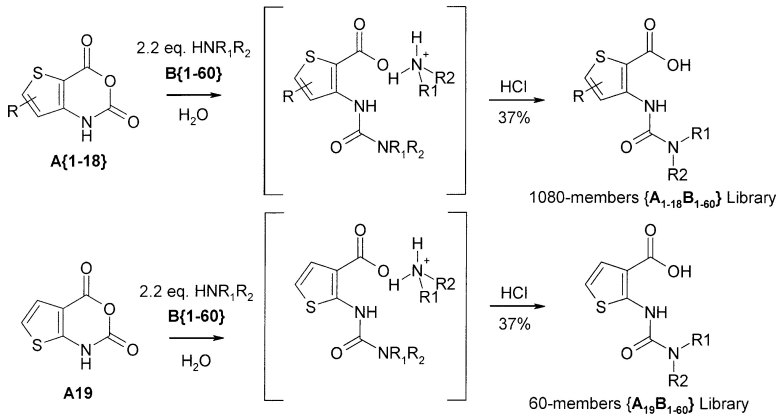
J. Comb. Chem., **2005**, 7 (2), 253-257• DOI: 10.1021/cc0498884 • Publication Date (Web): 15 January 2005



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Solution-Phase Parallel Synthesis of a 1140-Member Ureidothiophene Carboxylic Acid Library

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Received July 5, 2004

A 1140-library of thiophene ureidoacids was synthesized by the reaction of a set of 60 primary or secondary amines with a number of 19 thieno[3,2-*d*]- or thieno[2,3-*d*][1,3]oxazine-2,4-diones. All compounds were obtained by a simple solution-phase combinatorial strategy on a 200−400-mg scale with over 70% yields and purities over 80%. Sixty library members chosen at random were successfully characterized by standard ^{1}H NMR, HPLC/MS, and IR studies. Analgesic, antalgic, and antiinflammatory potential were investigated. The 1140-member ureidothiophene carboxylic acid library will be used in high-throughput screening assays.

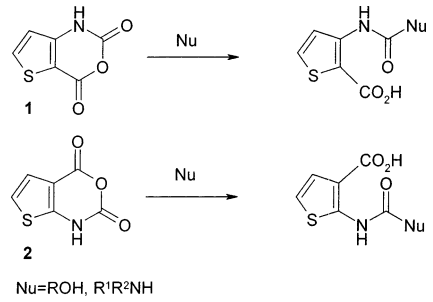
Introduction

Anthranilic acid and its activated form, isatoic anhydride, are useful building blocks for the synthesis of numerous heterocycles of therapeutic interest.[1,2] Although the thiophene ring is considered a bioisoster of the benzene ring, the synthesis and the chemistry of the thiophene analogues of isatoic anhydride remain very poorly studied.[3−5] Our laboratory recently developed an efficient synthesis of 1*H*-thieno-[3,2-*d*][1,3]-oxazine-2,4-dione **1** and 1*H*-thieno[2,3-*d*][1,3]-oxazine-2,4-dione **2** that we have termed thiaisatoic anhydrides.[6] We have studied the reactivity of **1** and **2** toward various nucleophiles, such as amines and alcohols, and have shown that nucleophilic attack proceeded exclusively on the carbamoyl moiety to lead to ureidoacids and carbamates, respectively (Scheme 1). Moreover, these building blocks can be used to synthesize new thieno[2,3-*d*]imidazol-2-ones,[7] thiophene analogues of benzimidazolones known for their interactions with CNS receptors and new pyrrolo[1,2-*a*]-thieno[3,2-*e*] and pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepines, which are thiophene analogues of antitumor pyrrolo[2,1-*c*]-[1,4]benzodiazepines.[8]

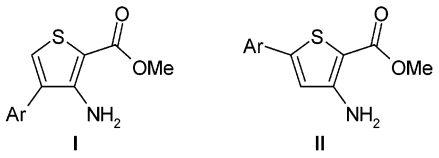
A desire to develop new heterocyclic libraries of potential therapeutic interest led to us taking advantage of the specific reactivity of thiaisatoic anhydrides to develop a solution-phase parallel synthesis of new thiophene ureidoacids of potential pharmaceutical interest as analgesic, antalgic, or antiinflammatory leads.

The first results of a solution-phase combinatorial approach of 6- and 7-arylthieno[3,2-*d*][1,3]-oxazine-2,4-diones with amines[9] allowed the application of our "parallelization" studies, leading to the solution-phase parallel synthesis of a 1140-member library of ureidothiophene carboxylic acids.

Scheme 1



Scheme 2



Results and Discussion

Building Block Synthesis and Initial Reactivity Studies. The thiaisatoic anhydride set **A**{*1*−*19*} were obtained from the corresponding methyl aminothiophene esters **I** and **II** prepared following known procedures (Scheme 2).[10−13] The alkaline hydrolysis of these aminoesters under microwave heating conditions led to the nonisolated amino carboxylate intermediates quickly, and phosgene addition permitted isolation of the corresponding anhydrides in high yields. Alkaline hydrolysis by conventional heating conditions required longer time, leading to degradation products because of the instability of amino carboxylate intermediates. Robba and colleagues had shown that enaminic-type delocalization made the ester function only slightly reactive under classical heating conditions.[14−16] Isolation of the intermediates was not necessary, since treatment with phosgene gave the expected anhydrides with yields of over 75%.

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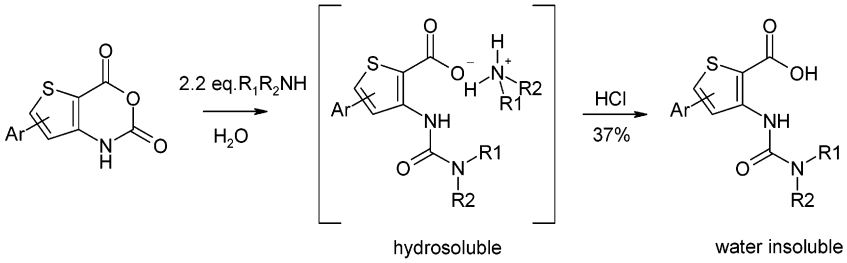
10.1021/cc0498884 CCC: $30.25
Published on Web 01/15/2005

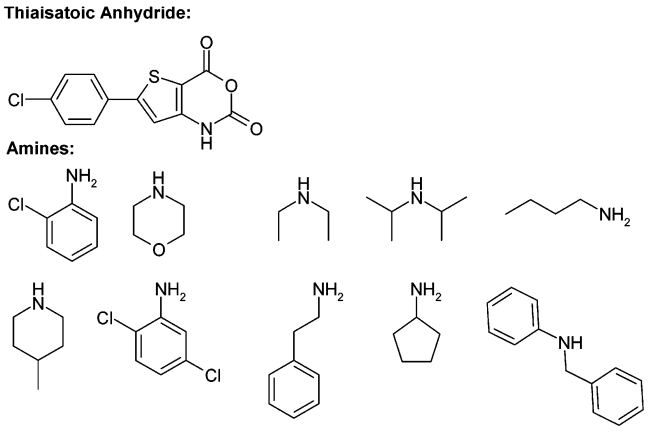
Scheme 3



"Parallelization" Concept and Synthetic Strategy. Despite the development of many workup procedures and purification methods for combinatorial solution-phase synthesis,[17−19] we chose an upstream strategy that consisted of the study of the reaction conditions in order to synthesize compounds of good purity in high yield without the use of tedious purification procedures, which would be incompatible with the synthesis of large libraries.

In our example, the bifunctionality and the reactivity of thiophene anhydrides allowed us to use an acid/base procedure for both the isolation and purification steps. This method was first used by Boger and colleagues for the generation of combinatorial libraries.[20] We first replaced the solvent of the reaction (THF) with water to eliminate the evaporation step. Under these conditions, a water suspension of the anhydrides reacted with 2.2 equiv of a primary or secondary amine and led to the water-soluble ammonium ureidothiophene carboxylates. The disappearance of the starting material allowed the reaction to be followed. The subsequent acidification of the reaction mixture allowed the ureidothiophene carboxylic acids to be precipitated as solids, which were filtered and straightforwardly washed with water, removing excess amines in the form of their water-soluble hydrochlorides (Scheme 3). To verify the repeatability of our procedure, a cross-validation procedure was realized with two experimental tests under the above conditions. The first one was the reaction of one anhydride with 10 representative primary or secondary amines (Chart 1), and the second one was the reaction of propylamine with 10 thiaisatoic anhydrides (Chart 2). In the two experiments, the average yield was up to 85%, and the identification and the purity of the crude products were determined by both ^{1}H NMR and LC/MS. In all cases, the identity of the compounds was confirmed, and the average purity was estimated to up to 85%.

Chart 1. Buildings Blocks Used for the First Verification of Reaction Strength and Repeatability



After validation, a library of more than 1000 ureidothiophene carboxylic acids was prepared in a solution-phase parallel synthesis with minimum technology and equipment, giving sufficient product (200−400 mg) for both in vivo and in vitro pharmacological evaluation. This simple optimization and simplification of the reaction procedure allowed use of classical equipment without automation!

Synthesis of the Library. The preparation of a larger ureidothiophene carboxylic acid library was next undertaken via this pathway (Scheme 3) and entailed the nucleophilic opening of 19 thiaisatoic anhydrides **A**{*1*−*19*} (Chart 3) with 60 commercially available primary or secondary amines **B**{*1*−*60*} (Chart 4). We chose to develop these syntheses

Scheme 4

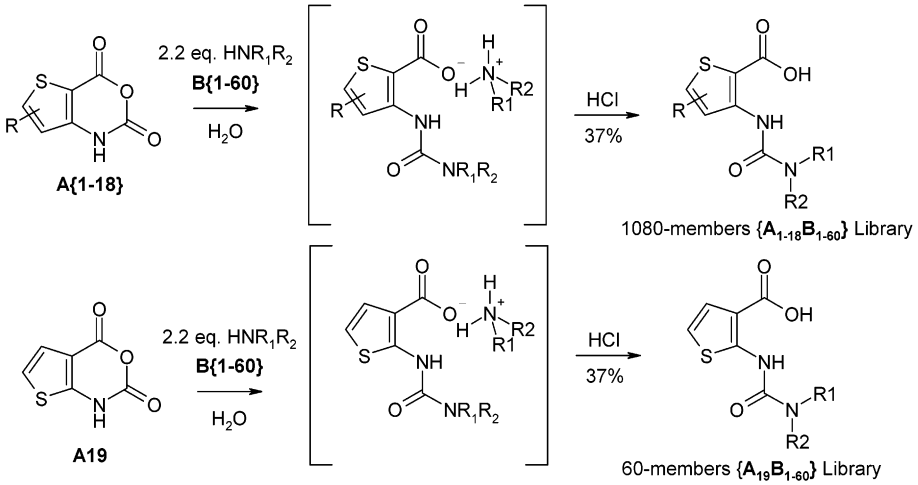
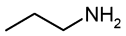


Chart 2. Buildings Blocks Used for the Second Verification of Reaction Strength and Repeatability

Amine:



Thiaisatoic Anhydride:

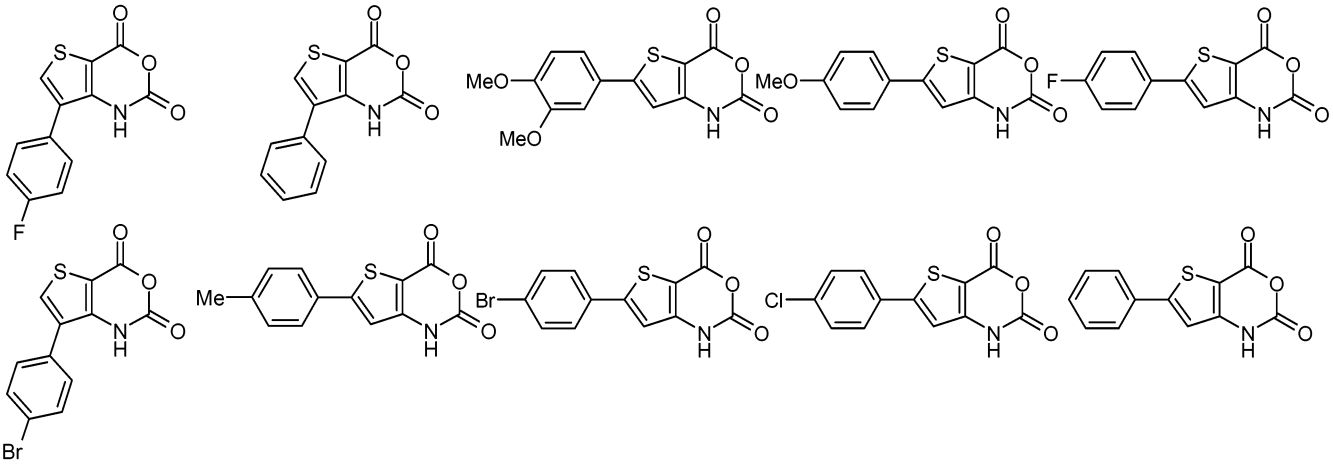
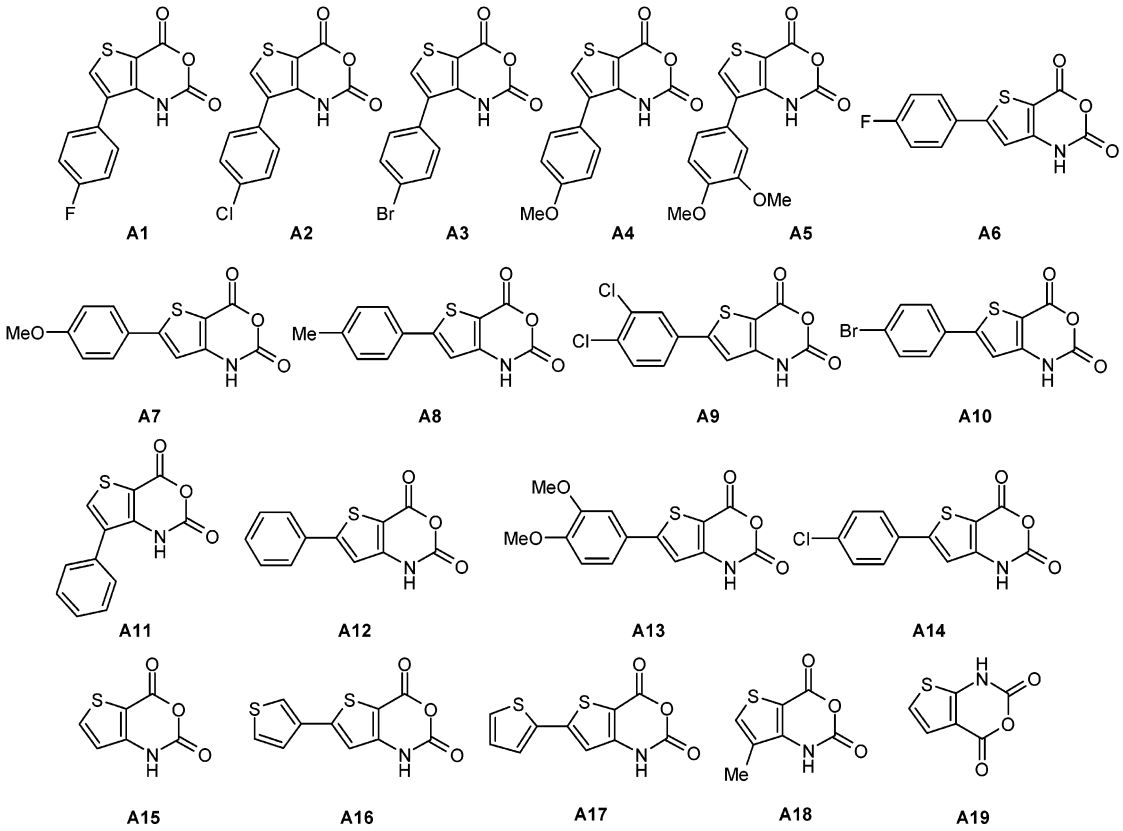


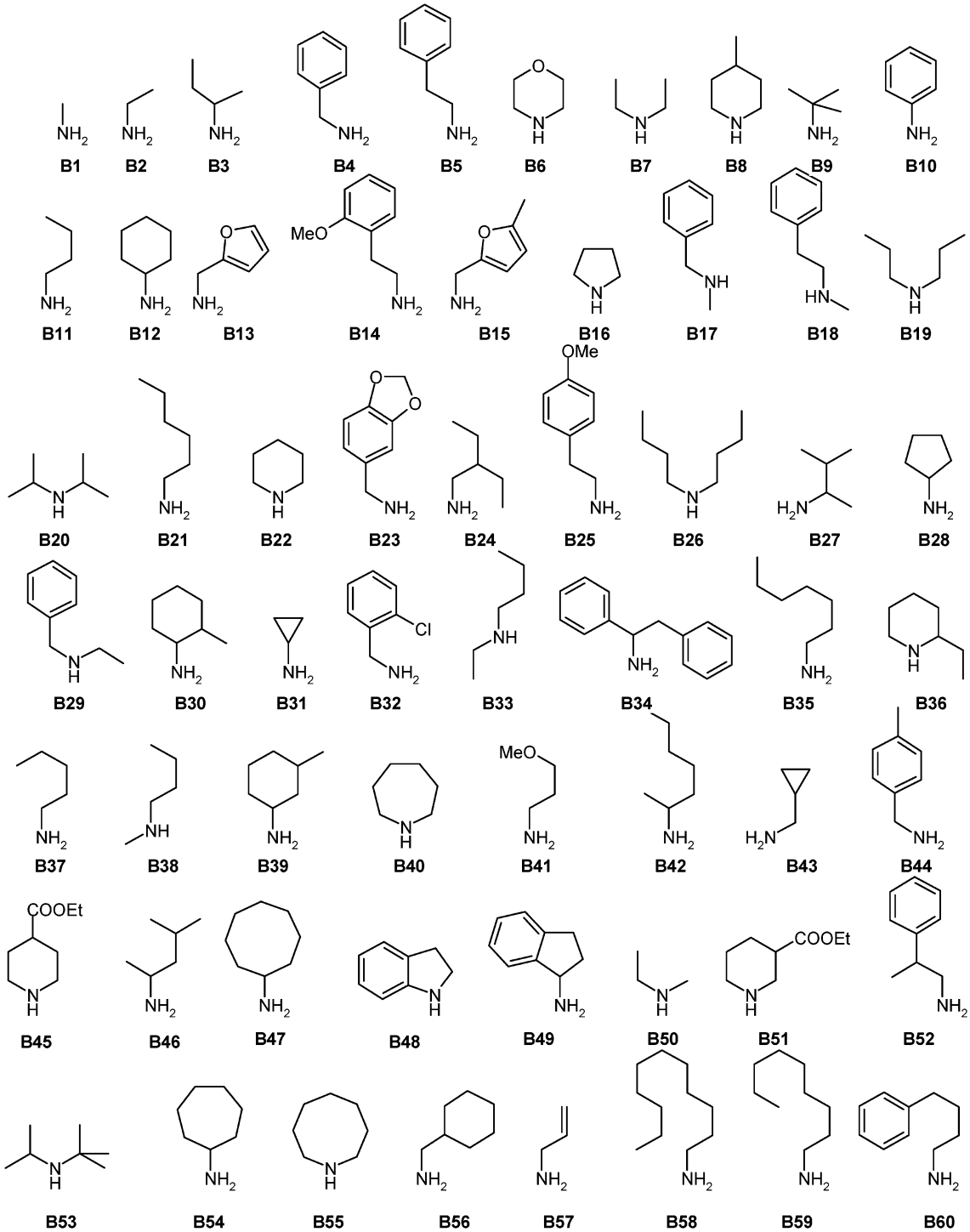
Chart 3. Set of Thiaisatoic Anhydrides A{*1*−*19*} for the Library



by 12 runs of 80 simultaneous reactions. In a typical run, the reactions of 8 thiaisatoic anhydrides and 10 amines were realized. 1 mmol of each of the eight anhydrides was dispersed into eight glass jars. Water (10 mL) was added to give an aqueous suspension of thiaisatoic anhydride, an efficient magnetic stirring was performed, and 2.2 mmol of primary or secondary amines was added. After 2 h, 37% hydrochloric acid was added, and the precipitate formed was filtered off and washed with water to give the ureidothiophene carboxylic acids. Yields for our experiment are presented below. Each library of 80 products was obtained in a 200−400-mg scale with yields over 70%. Reaction parallelization permitted us to develop rapidly a 1140-member library from which each compound could be used for different pharmacological screening.

Library Analytic Studies. The average molecular mass of the library was 371.08 g mol^{-1}, and its average cLogP was 1.99. To ensure high purity of the ureidothiophene carboxylic acids library, samples of the crude products were next analyzed by HPLC on an Xterra MS C_{18} column attached to an Alliance Waters separation module using an acetonitrile/water gradient. Average purity was over 90%,

Chart 4. Set of Amines B{*1*−*60*} for the Library



with 100% of the 60 analyzed products having purity above 80% (Table 2). Each derivative was obtained in a 200−400-mg scale, and a range of 60 compounds was characterized by LC/MS analysis. Positive and negative electrospray (ESI^+ and ESI^-) MS showed the presence of a single parent ion, which confirmed the identity of our selection of sample. In addition, ∼60 library members were chosen at random and successfully characterized by standard ^1H NMR studies. In the same way, 60 library members were selected at random, and ureidothiophene carboxylic acid carbonyl wavelengths were analyzed and compared with thiaisatoic anhydride. We noticed that if thiaisatoic anhydrides possessed a range of carbonyl wavelength between 1700 and 1800 cm^{-1}, thiophenic ureidoacids wavelength were situated between 1690 and

Table 1. Observed Yields for Our First Experiment

	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
A1	81	78	89	94	83	80	89	88	77	70
A2	75	81	89	73	83	100	86	70	79	79
A3	89	92	90	87	97	92	93	100	86	88
A4	75	81	74	84	94	74	77	77	80	84
A5	71	95	71	80	75	76	71	86	100	100
A6	81	100	100	93	88	87	100	97	100	79
A7	78	84	89	78	81	100	83	85	86	97
A8	71	75	82	85	84	82	90	76	90	85

Table 2. Analytical Data for 60 Compounds

compd	*m/z*	ESI^+	ESI^-	compd	*m/z*	ESI^+	ESI^-	compd	*m/z*	ESI^+	ESI^-
A7B1	306.33	307.07	305.06	A11B13	342.12	342.90	340.93	A9B38	400.47	400.80	399.80
A3B2	369.23	368.99	366.97	A4B14	426.05	426.85	424.85	A17B42	284.37	285.00	283.07
A10B2	368.93	369.97	368.95	A13B14	456.08	456.85	454.89	A3B43	396.02	396.78	394.79
A4B2	320.37	321.09	320.08	A2B15	390.12	390.85	388.83	A6B43	334.08	334.95	332.96
A3B3	397.27	397.02	ND[a]	A4B16	346.06	346.90	344.92	A10B45	480.11	480.72	478.80
A2B4	386.89	387.06	385.04	A16B18	386.17	386.89	384.91	A7B46	376.69	376.95	374.98
A6B4	370.39	371.08	369.07	A9B19	414.23	416.80	414.90	A6B52	398.21	398.94	396.97
A11B4	352.06	352.01	351.05	A14B20	383.09	383.84	ND[a]	A1B47	390.13	390.93	388.95
A16B4	357.82	358.79	356.86	A6B44	384.18	384.98	382.92	A12B49	358.19	ND[a]	357.17
A3B5	445.32	445.02	443.01	A16B21	352.05	352.93	350.95	A8B50	318.11	318.99	357.17
A8B5	380.46	381.13	379.11	A16B22	336.07	336.91	334.91	A14B50	338.61	338.92	336.93
A11B5	365.96	366.90	364.93	A4B23	430.41	430.82	428.89	A6B51	420.71	420.91	418.90
A1B6	350.36	351.10	349.04	A14B25	430.71	430.81	428.90	A7B52	409.71	410.87	408.91
A2B7	352.88	353.07	ND[a]	A12B27	332.17	332.94	330.98	A11B52	380.21	380.91	380.90
A4B8	374.46	375.20	373.10	A18B28	368.65	369.04	367.06	A15B55	282.20	283.05	281.07
A2B9	352.87	353.07	351.07	A12B30	358.20	358.95	356.95	A19B55	364.20	364.88	362.94
A5B9	378.43	379.13	377.12	A10B31	380.99	382.75	379.89	A2B56	392.70	392.85	390.88
A3B10	417.27	416.99	ND[a]	A14B32	422.10	422.76	420.80	A11B58	416.33	416.96	415.01
A7B10	368.71	369.09	ND[a]	A6B35	378.12	378.96	376.99	A2B59	423.77	424.90	422.97
A7B13	371.88	372.90	370.89	A14B38	366.66	366.89	364.93	A8B60	408.24	408.91	406.96

[a] Not determinated.

1620 cm^{-1}. The reaction was successful in tolerating a wide diversity of functional groups with the desired product formed in every reaction. Supporting Information contains copies of the LC/MS and spectroscopic data.

Conclusions

A practical and efficient synthetic strategy to synthesize a library of ureidothiophene carboxylic acids has been developed. The parallelization strategy has been successfully used for the solution-phase preparation of a 1140-member ureidothiophene carboxylic acid library (19 × 60). Each compound was obtained in a 200−400-mg scale and with over 70% yield. Samples of the compounds were characterized by LC/MS analysis and various spectroscopic studies (^{1}H NMR, IR). Biological evaluation of this library is currently under progress. Moreover, further investigations in parallelization procedures are currently being developed by our laboratory to apply this concept for quick solution-phase synthesis in a large number of various heterocyclic libraries.

Acknowledgment. This work was supported by the Conseil Régional de Basse-Normandie, the PUNCHorga (Pôle Universitaire Normand de Chimie Hétérocyclique et Organique), the Actions Concertées Incitatives (A.C.I.) and the F.E.D.E.R. (Fonds Européens de Développement Economique Régional). We are thankful to Pr. Lazdunski and Dr. Michel Boulouard for the first pharmacological studies.

Supporting Information Available. Experimental procedures and characterization data for samples covering 6% of the library. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC0498884